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Physostigmine's effect on diminished fetal heart rate variability caused by scopolamine, meperidine and propiomazine

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Fetal heart rate (F.H.R.) variability has been recognized for many years as a useful guide in assessing fetal well being [4]. While normal fetal heart rate variability is associated with fetal health, a loss of this variability, especially when associated with late deceleration or severe variable deceleration patterns, has been shown to be an omnious sign of fetal distress [2]. Since drugs such as meperidine, propiomazine and scopolamine often result in a loss of fetal heart rate variability [1], secondary to their central autonomic suppression, this parameter of fetal heart rate monitoring often cannot be assessed accurately when these drugs are present in the patient in labor. Because of this, it might be beneficial to attempt to reverse this drug induced loss of fetal heart rate variability if, during labor, confusion arose as to its importance in assessing fetal distress. Since physostigmine can be used to reverse the delirium resulting when scopolamine is given to an adult [3] and since it is a drug well known for its anticholinesterase activity, physostigmine was given to patients in labor previously given scopolamine alone and meperidine and propiomazine in combination to ascertain the effect on reversing the loss of fetal heart rate variability caused by the administration of these drugs.

Materials and methods

Seventeen healthy women between 39 and 42 weeks gestation in early labor who had received no medication previously were utilized for this study. The age range of the patients studied was 15 to 33 while parity and range was 0 to 3. Patients were screened for allergies to drugs as well as history of asthma because of physostigmine's potential adverse effect in patients with these problems. Internal fetal heart rate monitoring was accomplished by the use of a scalp electrode attached to a fetal monitor* after artificial or spontaneous rupture of the amniotic membranes. Maternal blood pressure and pulse were recorded at two minute intervals and base line fetal heart rate variability was recorded and classified as previously described [1]. All patients were noted

* Corometrics – Wallingford, Conn.

Curriculum vitae

FRANK H. BOEHM, *M.D. was born in Nashville, Tennessee in 1940. He was graduated from Vanderbilt University, Nashville, Tennessee in 1962 and received his M.D. from Vanderbilt University Medical School in 1965. His OB-GYN residency was completed in 1970 at Yale-New Haven Hospital, New Haven, Connecticut. He is now Associate Professor and Director of the Fetal Intensive Care Unit at Vanderbilt University Hospital. His major interests are High Risk Obstetrics, Fetal Monitoring and Regionalization of Perinatal Health Care.*

to display normal fetal heart rate variability prior to drug administration. Total scopolamine doses of 0.65 to 1.08 mgs was given intravenously to 7 patients followed by 2 to 5 mgs of physostigmine intravenously after establishing a decrease of fetal heart rate variability. This same procedure was followed in 10 patients after administration of meperidine, 50 mgs, and propiomazine, 20 mgs, intravenously. Maternal blood pressure, pulse, as well as fetal heart rate variability was then assessed for 60 minutes following the infusion of physostigmine.

Results

Scopolamine in doses of 0.65 to 1.08 mgs diminished fetal heart rate variability in all 7 patients and physostigmine reversed this loss of fetal heart rate variability in all 7 patients within 4 to 17 minutes (average 9 min.) (Tab. I, Figs. 1–3). No remarkable maternal blood pressure changes were recorded after administration of physostigmine in the 7

Tab. I. Total doses of drugs with time to effect from first dose of physostigmine.

Name	Scopolamine (total dose)	Physostigmine (total dose)	Time to effect from 1st. dose
B.G.	0.65 mg	5 mg	4 min
L.S.	1.08 mg	2 mg	7 min
S.B.	0.65 mg	4 mg	11 min
J.B.	1.08 mg	4 mg	8 min
V.H.	.65 mg	4 mg	12 min
B.C.	1.08 mg	4 mg	17 min
R.U.	.65 mg	2 mg	5 min

Name	Meperidine/ Propiomazine (total dose)	Physostigmine (total dose)	Time to effect from 1st. dose
J.W.	50 mg/20 mg	4 mg	7 min
V.B.	50 mg/20 mg	3 mg	8 min
M.J.	50 mg/20 mg	3 mg	4 min
T.Y.	50 mg/20 mg	3 mg	11 min
G.S.	50 mg/20 mg	3 mg	9 min
C.S.	50 mg/20 mg	3 mg	3 min
P.R.	50 mg/20 mg	3 mg	17 min
R.C.	50 mg/20 mg	3 mg	7 min
C.D.	50 mg/20 mg	3 mg	12 min
B.P.	50 mg/20 mg	3 mg	13 min

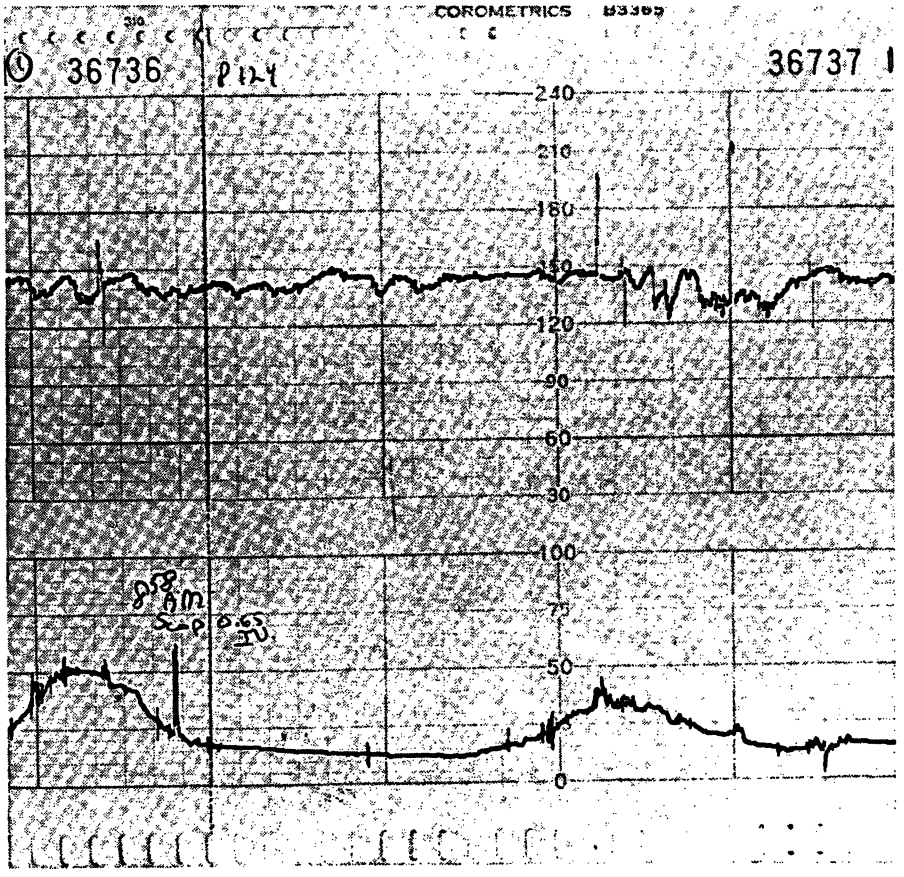


Fig. 1. Fetal heart rate tracing revealing normal variability prior to scopolomine infusion.

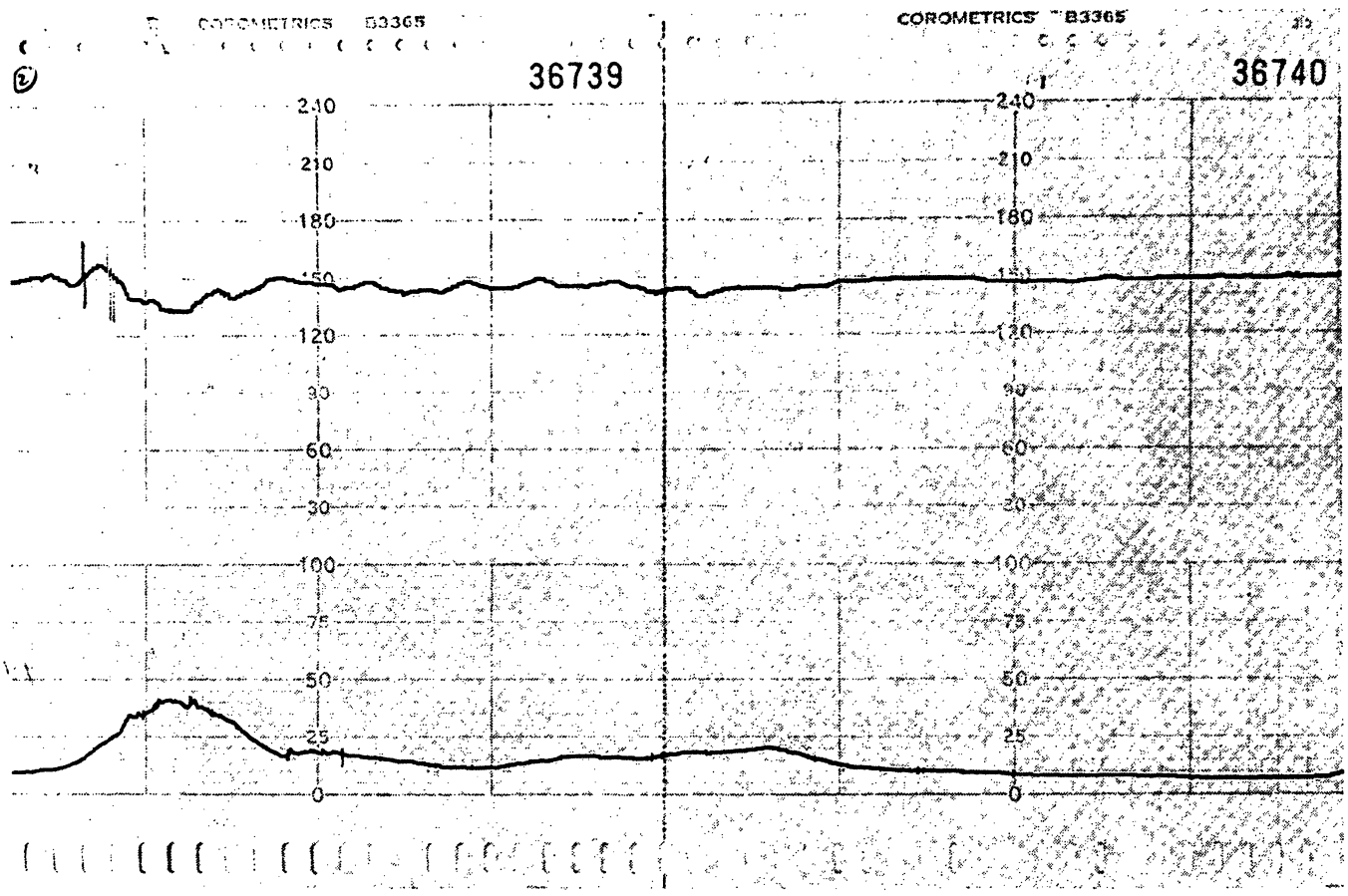


Fig. 2. Fetal heart rate tracing revealing loss of variability after scopolomine infusion.

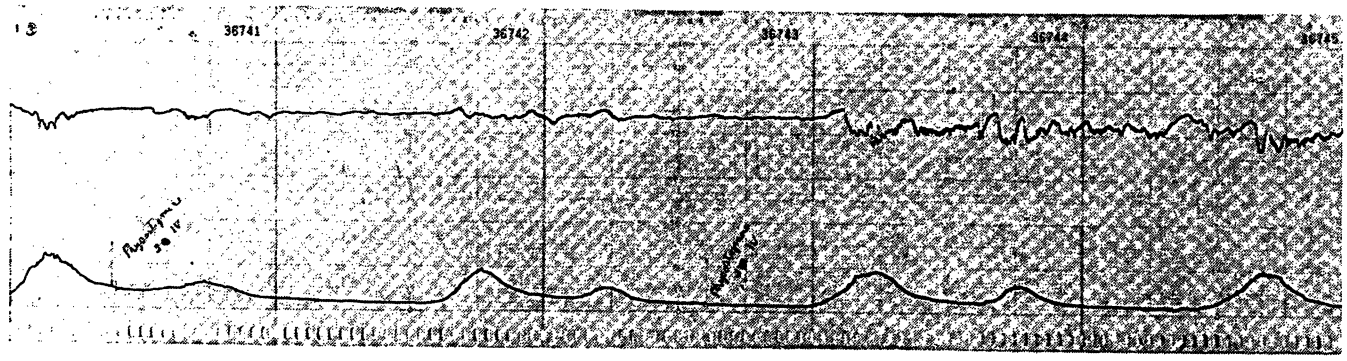
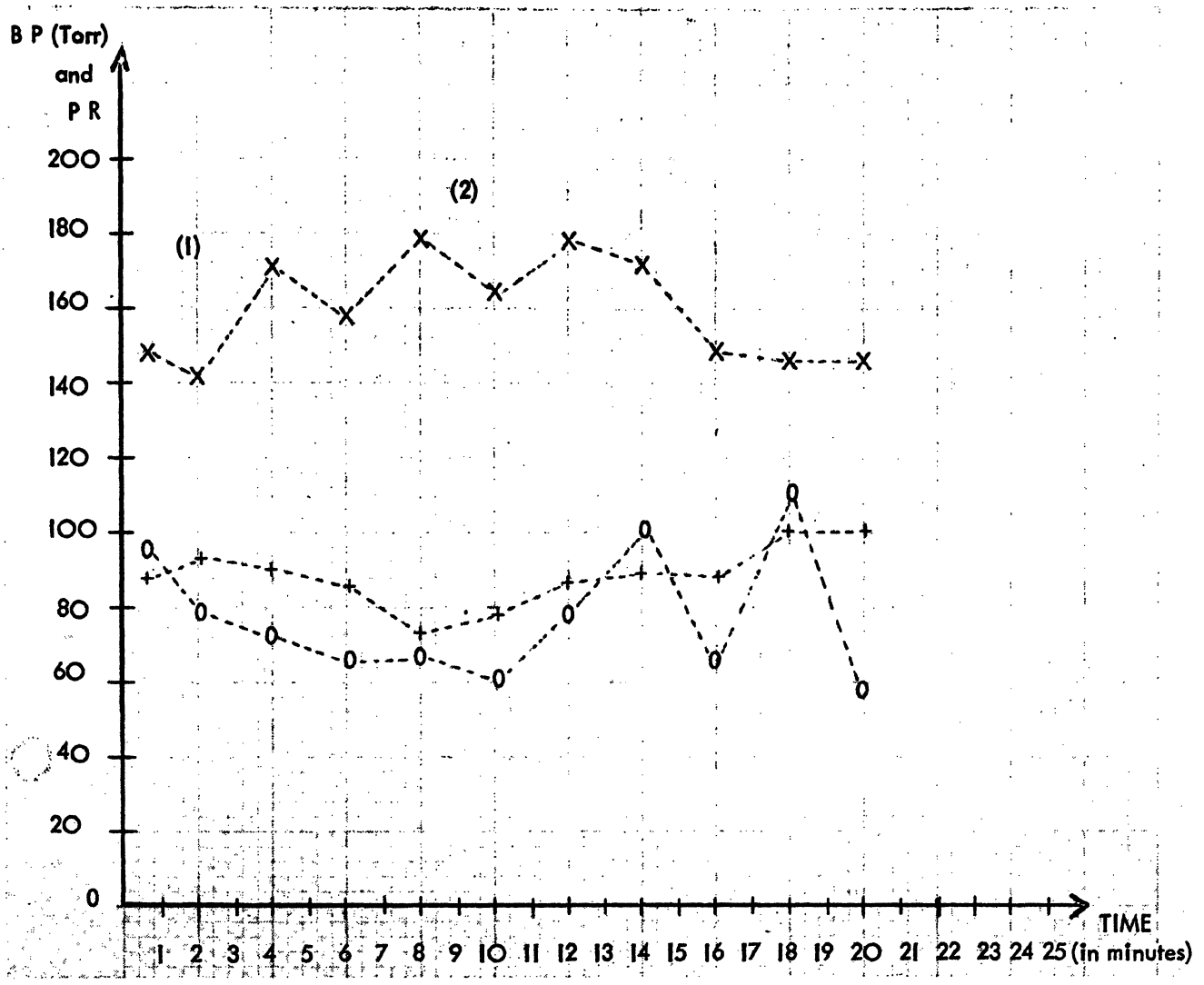


Fig. 3. Fetal heart rate tracing revealing abrupt return to normal variability 11 minutes after infusion of the first 2 mg dose of physostigmine.

patients studied although 1 patient did sustain an elevation of 40 mm Hg in systolic pressure which returned to the base line within 14 minutes (Fig. 4). Maternal pulse rate, already elevated slightly by scopolamine, was reduced to 56 beats per minute in 1 patient (Fig. 4). No adverse systemic reactions to either scopolamine or physostigmine was noted in any of the patients. Fetal scalp samples obtained within 10 minutes after physostigmine administration was performed in 2 patients and were found to be within normal limits, however no further attempts were made to follow fetal scalp pH because of fetal manipulation effects on fetal heart rate variability. No pathological fetal heart rate patterns



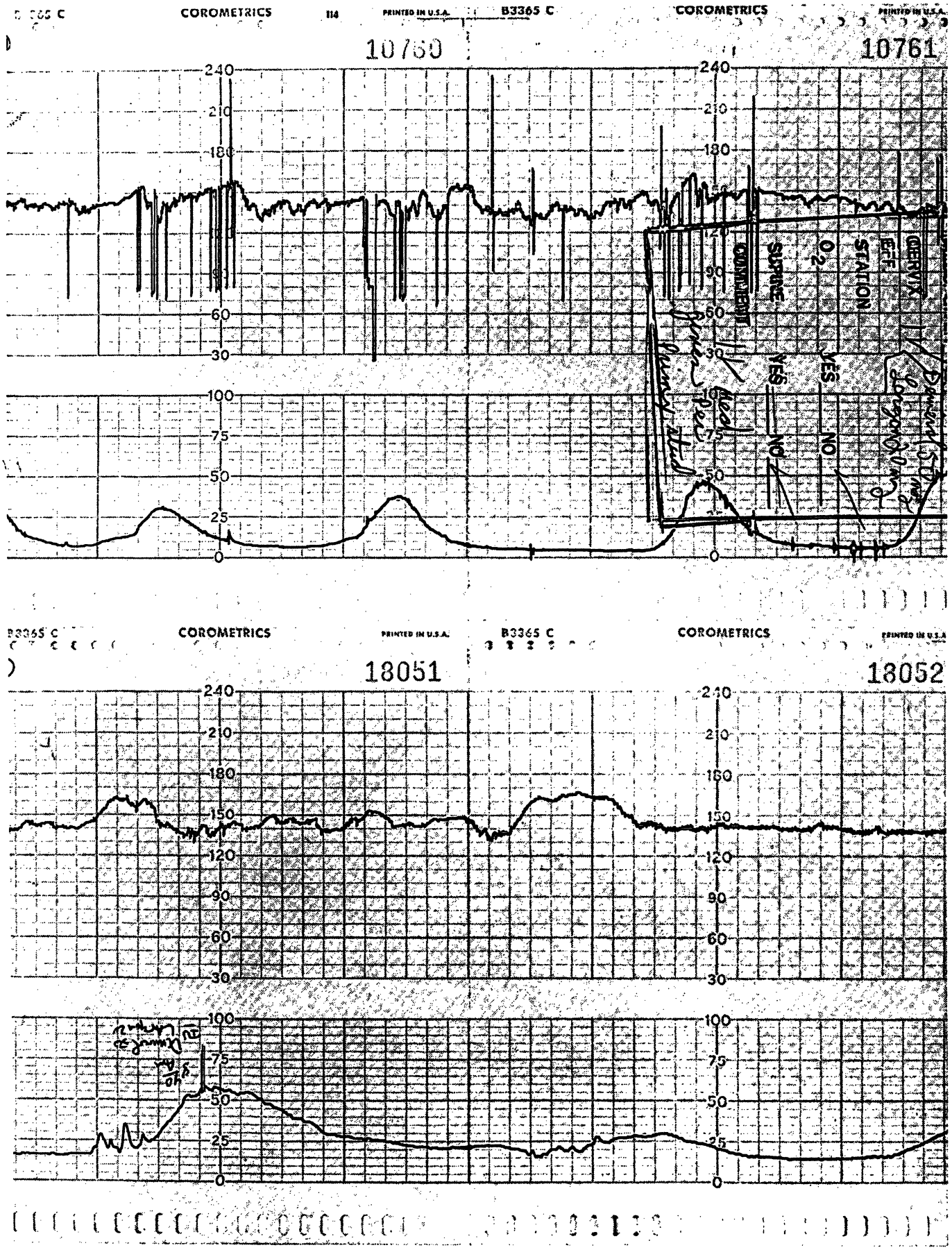
PATIENT NO : 5
MATERNAL B P (blood pressure) and P R (pulse rate) changes related in TIME following physostigmine administration.

X : B P (systolic)
\+ : B P (diastolic)
0 : P R (pulse rate)
(1) : following the first dose of physostigmine of 2 mg., intravenously.
(2) : after the second dose of physostigmine of 2 mg., intravenously.

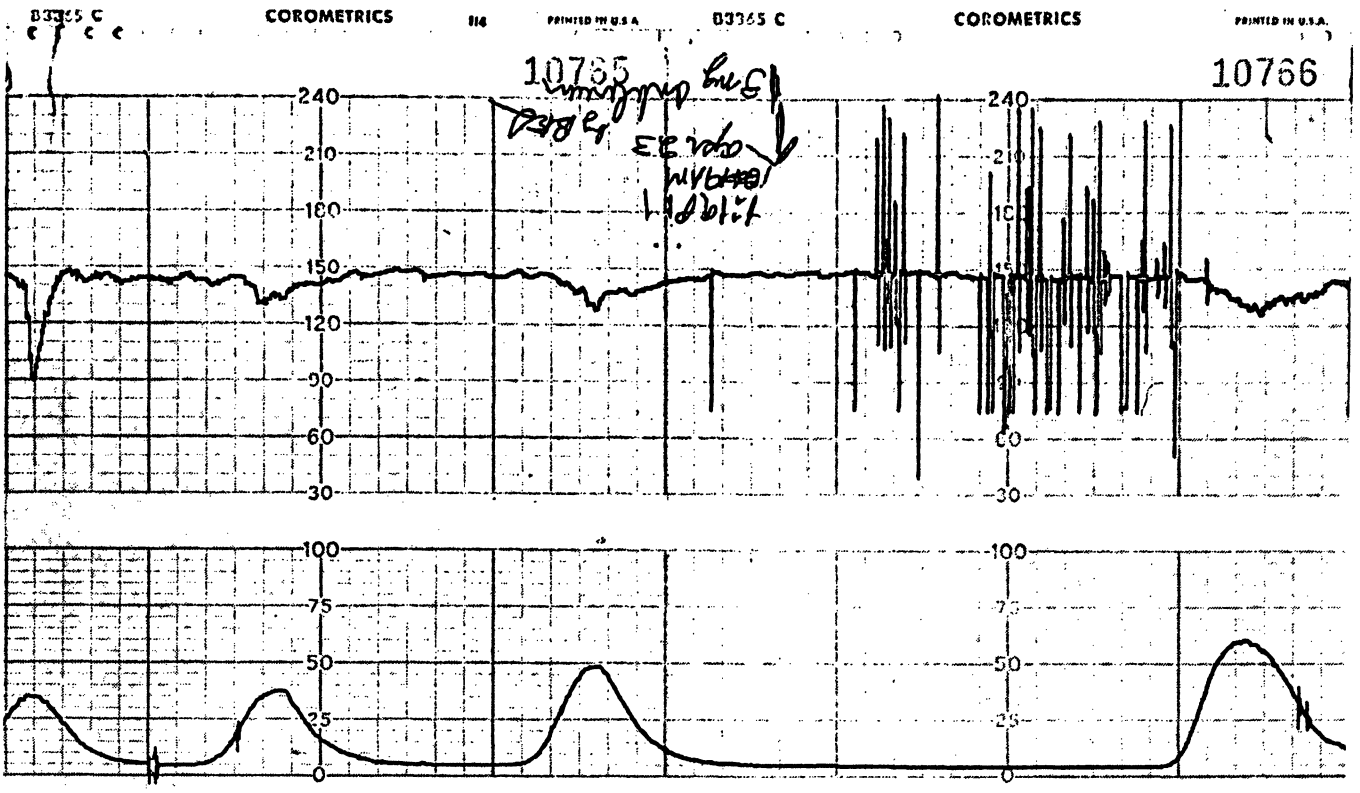
Fig. 4. Graph depicting a rise in systolic blood pressure and a fall in maternal pulse rate.

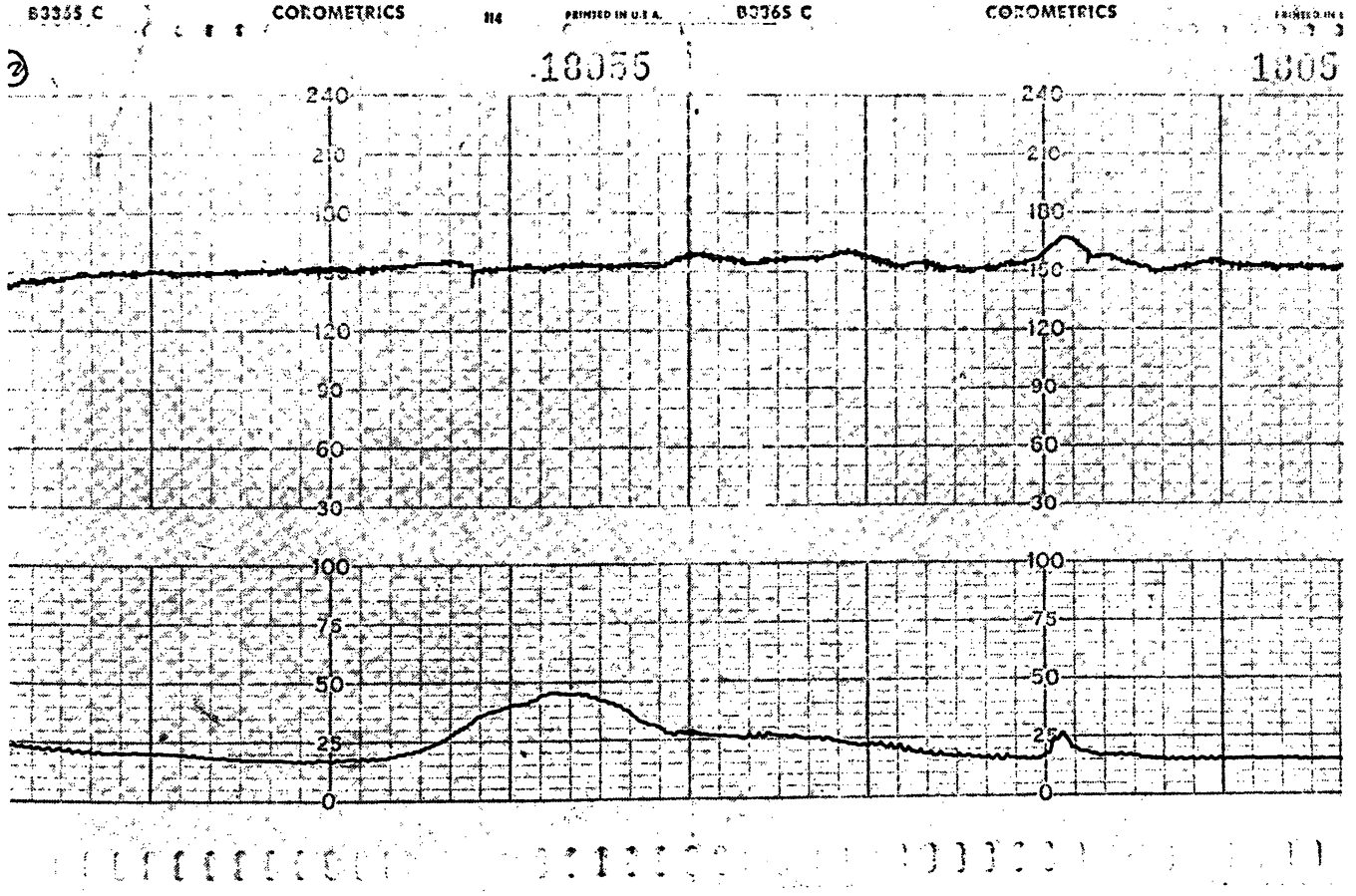
or significant fetal heart rate base line changes were recorded during the study. All patients delivered normal term neonates with 5 minute Apgar scores of 8, 9 or 10.

The 10 patients who were given meperidine and propiomazine whose fetal heart rate variability was diminished sufficient to ascertain physostigmine's effect were noted to show an increase in fetal heart rate base line variability within 3 to 17 minutes (average 9.1 min.) after the administration of 3–4 mgs of physostigmine intravenously (Tab. I, Figs. 5–10). While one patient's pulse decreased 40 beats per minute within 5 minutes of physostigmine's infusion, no patient's pulse rate fell below 60 beats per minute. Most pulse rates remained stable, fell slightly, or occasionally

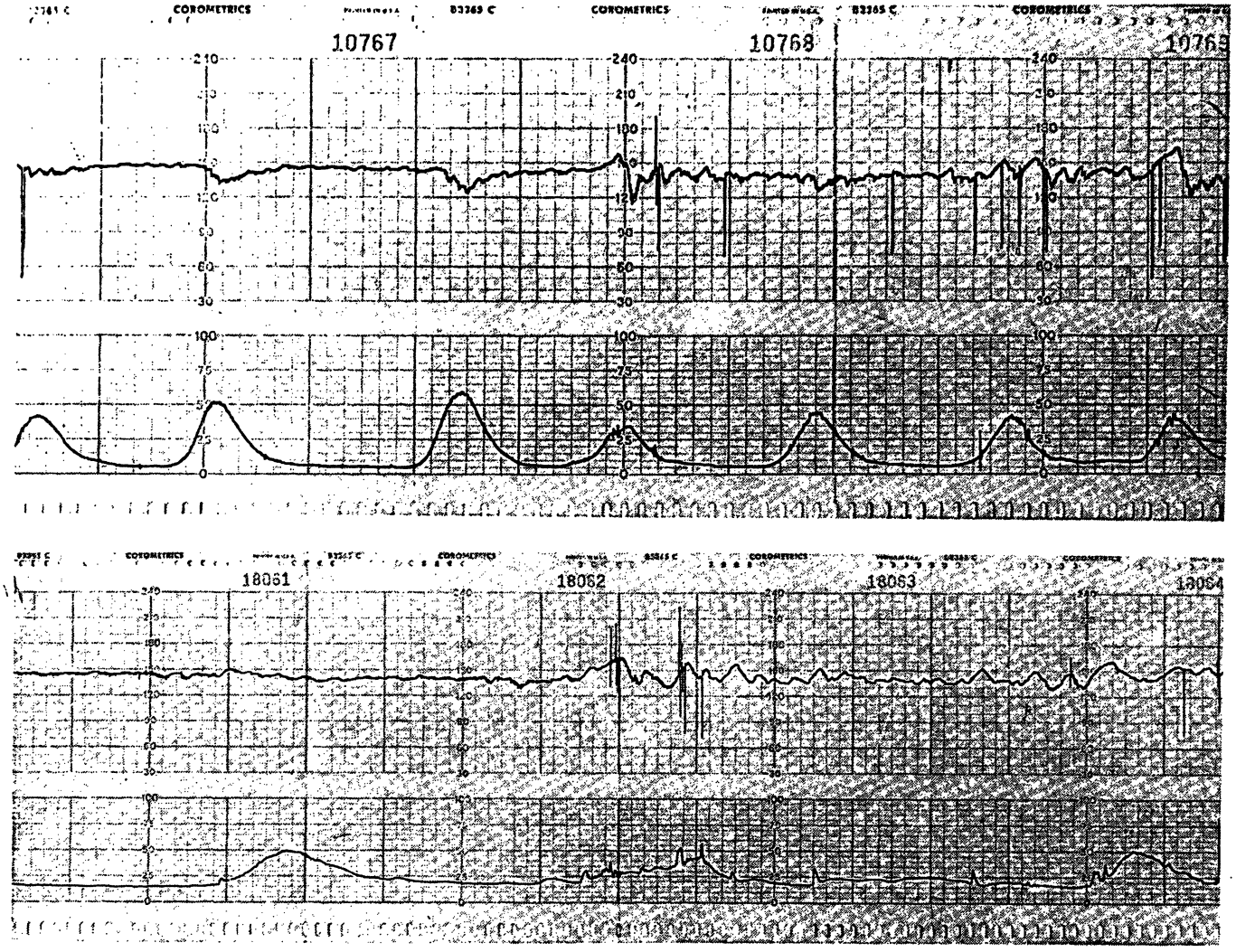


Figs. 5 & 6. Fetal heart rate tracings revealing normal variability prior to meperidine and propiomazine infusions.





Figs. 7 & 8. Fetal heart rate tracings revealing loss of variability after administration of meperidine and propiomazine.



Figs. 9 & 10. Fetal heart rate tracings revealing abrupt return to normal variability minutes after physostigmine infusion.

were noted to be elevated following physostigmine infusion. There were no significant blood pressure changes recorded in this group of patients. Again, no pathological fetal heart rate patterns were recorded any time during the study and all patients delivered normal term neonates with 5 minute Apgar scores of 8, 9 or 10.

Comments

Physostigmine, an anticholinesterase drug and capable of crossing the blood brain barrier, has been noted to be able to reverse the delirium produced by atropine like drugs [3]. Its effect, however, on fetal heart rate variability has not been previously studied. It seems tenable from this study that physostigmine does cross the placental barrier and enters the fetal circulation and that this usually occurs within 3 to 17 minutes with an average of approximately 9 minutes. The possibility of utilizing this drug to determine placental function in the future is intriguing. In the healthy fetus the loss of fetal heart rate variability caused by scopolamine, meperidine or propiomazine can be reversed by the use of physostigmine and this reversal seems abrupt and clinically measurable on the fetal monitor print out. Maternal responses to blood pressure and pulse after infusion of physostigmine are minimal and are in agreement with other studies. SMILER, et al. recorded no adverse effects of physostigmine in doses of 3 mg intravenously on the fetus or mother and noted no fetal or maternal bradycardia [3]. Maternal bradycardia (less than 50 beats per minute) was not

noted in any of our patients studied, however, one was noted to have a pulse rate of 56 beats per minute. This patient was given a total of 4 mg of physostigmine. **The fact that physostigmine can reverse the loss of fetal heart rate variability caused by meperidine and propiomazine support the fact that such depression of fetal heart rate variability caused by these drugs may be based on their atropine like properties.**

Studies to ascertain physostigmine's effect on fetal heart rate variability in animals who are noted to display loss of fetal heart rate variability secondary to induced fetal distress will need to be performed in the future. If no such return of fetal heart rate variability is noted in this experimental situation it would seem tenable to use the drug, physostigmine, as a clinical test to distinguish the fetus in distress from one whose fetal heart rate variability is diminished secondary to drug administration. Therefore, in the sedated patient who displays a questionable pathological fetal heart rate deceleration, a quick return to normal variability after administration of physostigmine, might obviate the need for fetal scalp sampling or other obstetrical intervention. Because physostigmine might cause further physiological embarrassment in the already acidotic or hypoxic situation, human use to differentiate fetal distress from drug effect is not recommended until further studies have clarified this possibility.

Summary

Physostigmine was given to 17 patients in labor, previously given scopolamine alone or meperidine and propiomazine in combination, to ascertain its effect on reversing the loss of fetal heart rate variability caused by the administration of these drugs. The results of the study indicated that scopolamine in doses of 0.65 to 1.08 milligrams diminished fetal heart rate variability in all 7 patients and physostigmine reversed this loss of fetal heart rate variability in all 7 patients within 4 to 17 minutes after injection of the first dose of physostigmine. Similar results were noted in 10 patients with the combination of meperidine, 50 mg, and propiomazine, 20 mg. It seems tenable from this study that physostigmine does cross the placental barrier and enters the fetal circulation and that this usually occurs within 3 to 17 minutes with an average of approximately 9 minutes. **In the healthy fetus the loss of fetal heart rate variability caused by scopolamine, meperidine or propiomazine can be reversed by the use of physostigmine and this reversal seems abrupt and clinically measurable on the fetal monitor print out.**

Keywords: Anticholinesterase, fetal distress, monitoring, physostigmine, placental barrier, variability.

Zusammenfassung

Der Einfluß von Physostigmin auf die durch Scopolamin-, Meperidin- und Propiomazininduzierte Verminderung der Schlag-zu-Schlag-Variabilität der FHF

Bei 17 Patientinnen, die kurz zuvor Scopolamin alleine oder Meperidin oder Propiomazin zusammen erhalten hatten, wurde subpartual Physostigmin gegeben. Ziel war es, den Neutralisationseffekt auf den Fluktuationsverlust der FHF, der durch Applikation der genannten Medikamente ausgelöst worden war, zu sichern. Die Resultate dieser Untersuchung zeigen, daß Scopolamin in einer Dosierung von 0,65 bis 1,08 mg bei allen 7 Patientinnen die Schlag-zu-Schlag-Variabilität negativ beeinflußte und das Physostigmin diesen Fluktuationsverlust der FHF bei allen 7 Patientinnen innerhalb von 4–17 Min. nach Injektion der 1. Dosis aufzuheben imstande war. Analoge Resultate konnten bei 10 Patientinnen, die Meperidin 50 mg und Propiomazin 20 mg erhalten hatten, beobachtet werden. Es scheint auf Grund dieser Untersuchungen erwiesen, daß Physostigmin die Plazentaschranke passiert und in den fetalen Kreislauf übertritt; dies geschieht in der Regel innerhalb von 3–17 Minuten, wobei der Mittelwert ungefähr 9 Min. beträgt. **Der durch Scopolamin, Meperidin und Propiomazin hervorgerufene Fluktuationsverlust der FHF kann beim gesunden Fetus durch Gabe von Physostigmin aufgehoben werden;** diese Wiederherstellung erfolgt rasch und kann klinisch auf den Kardiotokogrammen dokumentiert werden.

Schlüsselwörter: Anticholinesterase, fetal distress, FHF-Überwachung, Physostigmin, Placenta-Schranke, Schlag-zu-Schlag-Variabilität.

Résumé

Effet de la physostigmine sur la baisse de variabilité de la fréquence cardiaque foetale causée par la scopolamine, la mépéridine et la propiomazine

17 malades traités en laboratoire avaient reçu de la scopolamine seule ou un mélange dosé de mépéridine et de propiomazine, à la suite de quoi on leur a administré de la physostigmine pour observer ses effets sur le revirement de perte de variabilité de la fréquence cardiaque foetale causée par la prise des médicaments précités. Les résultats des examens ont montré que la scopolamine appliquée à doses de 0,65 à 1,08 milligrammes fait baisser la variabilité de la fréquence cardiaque foetale chez les 7 malades et que la physostigmine a renversé cette baisse chez les 7 patientes dans l'espace de 4 à 17 minutes après l'injection de la première dose de physostigmine. Des résultats similaires ont été observés chez les 10 malades ayant reçu un mélange de 50 mg de mépéridine et de 20 mg de propiomazine. Cette étude laisse supposer que la physostigmine traverse la barrière placentaire pour pénétrer dans la circulation foetale et cela, généralement, entre 3 et 17 minutes, la moyenne étant de 9 minutes environ. **Chez le foetus sain, la perte de variabilité de la fréquence cardiaque foetale, causée par la scopolamine, la mépéridine ou la propiomazine, peut être renversée par l'administration de physostigmine, et ce revirement semble s'opérer de façon assez brusque et peut être mesuré cliniquement sur l'enregistrement par moniteur du foetus.**

Mots-clés: anticholinestérase, barrière placentaire, distress foetal, monitoring, physostigmine, variabilité

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